APPENDIX A: DETAILED INCLUSION AND EXCLUSION CRITERIA AND DEFINITION OF LIVER CIRRHOSIS ADOPTED

STOP-HCV cirrhosis study participants were recruited from secondary care hepatology clinics in the UK. All individuals meeting the following two criteria were invited to participate:

I. Attendance at one of 31 participating UK liver clinics for care/management of HCV infection between Jan 2015 and July 2016
II. Diagnosed with liver cirrhosis at the time of attendance (definition provided in Appendix A)

Patients were ineligible if they: (i) were not previously enrolled into HCVRUK and did not consent to being concurrently enrolled into HCVRUK; (ii) were actively waiting for a liver transplant; (iii) had an isolated portal vein thrombosis; or (iv) were unable to provide informed written consent.

The definition of liver cirrhosis adopted in this study was as follows:

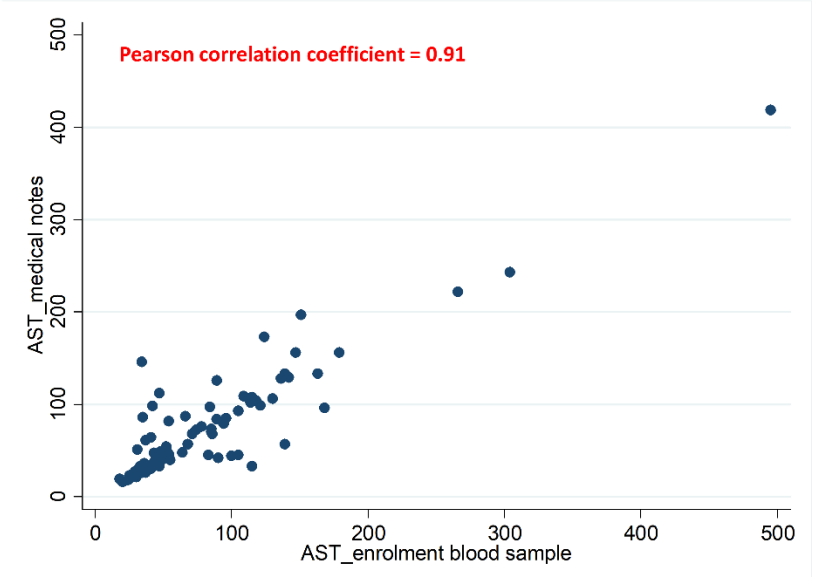
1) Histological assessment suggesting cirrhosis (Ishak 5/6 or Metavir 4).
   OR
2) Imaging result consistent with liver cirrhosis, including
   a. Fibroscan with a reading greater than 15kPa
   b. Evidence of varices at endoscopy in the context of a patent portal vein
   c. Definitive radiological evidence of cirrhosis (i.e. nodularity of liver and splenomegaly on ultrasound/CT.

   OR
3) A validated serum biomarker consistent with liver cirrhosis, including
   a. APRI >2
   b. Fibrotest >0.73
   c. ELF score >10.48

APPENDIX B: CALCULATION OF VALIDATED BIOMARKER VALUES

Validated biomarker values were calculated from the most recent test conducted prior to enrolment. Tests carried out more than 12 months before study recruitment were excluded. Preliminary analysis of the laboratory data at enrolment highlighted that 34% (404/1196) were missing a result for aspartate aminotransferase (AST), which is a critical parameter for calculating APRI, FIB4 and ALBI-FIB4 biomarkers. Thus, we used residual blood sample collected at enrolment to measure AST, if a value could not be found in a participant's medical records. This brought the level of participants missing AST data down to <10% (79/1196). In parallel, we also measured AST in a smaller random subgroup (N=90) of participants who *did* have an AST value recorded in their medical records to verify that the two sets of results were concordant. As expected, we saw a very strong correlation between these two sets of results, which is illustrated in the figure below.

Appendix Figure 1. concordance between most recent AST recorded in medical records and AST measured from enrolment blood sample (N=90)



Validated biomarkers were calculated using the following formulae:

1. APRI=(AST/40)/Platelet count.

   Where AST and ALT are measured in IU/L, and platelet count is measured in number per 10^9/L

2. FIB4=(age*AST)/(Platelet count*sqrt(ALT))

   Where AST and ALT are measured in IU/L, and platelet count is measured in number per 10^9/L

3. ALBI=(0.66*$\log_{10}$(bilirubin))+(-0.085*albumin)

   Where bilirubin is measured in µmol/L; albumin is measured in g/L [1].

4. ALBI-FIB4=(ALBI*1.331)+(FIB-4*0.165)

   Where, ALBI and FIB-4 were defined according to the formulae above.[2]

5. MELD= 4.082*$\log_e$(bilirubin) +8.485*$\log_e$(creatinine)+10.671*$\log_e$(INR)+7.432.

   Where, bilirubin and creatinine levels are measured in mg/dl

   N.B. the following adjustments were made to bilirubin, creatinine and INR, before calculating MELD: [3,4].

   (i) Bilirubin values <1 were replaced with a value of 1.
   (ii) Creatinine values <1 and >4 were replaced with a value of 1 and 4, respectively.
   (iii) INR values <1 and >3 were replaced with a value of 1 and 3, respectively.

6. MELD_Na= MELD+(1.32 *(137-sodium))-(0.033*MELD*(137-sodium))

MELD is calculated from the formula described above.

Sodium is measured in units of mEq/L. N.B. sodium values <125 and >137 were replaced with values of 125 and 137, respectively, before applying this formula.

7. CTP=Albumin+Bilirubin+INR+Ascites+Encephalopathy

Where albumin=1 if >3.5; 2 if 2.8-3.5; and 3 if <2.8 mg/dl.

Bilirubin=1 if <20; 2 if 20-29; and 3 if ≥30 mg/dl

INR=1 if <1.7; 2 if 1.7-2.3; and 3 if >2.3

Ascites=1 if absent; 2 if grade 1-2; and 3 if grade 3-4

Encephalopathy=1 if absent; 2 if grade 1-2; and 3 if grade 3-4.

APPENDIX C: CALCULATION OF GENETIC RISK SCORES

SEVEN GENE SIGNATURE (Huang et al "Cirrhosis risk score")

The 7 Gene cirrhosis risk score was developed by Huang et al in 2007 to stratify patients with chronic HCV according to their risk of liver cirrhosis.[5] Independent validation studies confirm that this score is associated with progression of HCV-related liver disease. [6,7] In the present analysis, we assessed if this risk score is useful for stratifying cirrhosis patients in terms of their future prognosis. The 7 gene risk score is calculated from 7 polymorphisms (see table below).

rsID	Chr	Gene	Risk genotype
rs62522600	8	*AZUB1*	GG
rs4986791	9	*TLR4*	CC
rs886277	11	*TRPM5*	CC/CT
rs2290351	15	*AP3S2*	AA/AG
rs4290029	1	*B008027*	GG
rs17740066	3	*STXBP5L*	AA/AG
rs2878771	12	*AQP2*	GG

We applied the weightings described by Huang et al[5] to calculate this score for each participant.

INNES-BUCH GENETIC RISK SCORE:

The Innes-Buch GRS is a summary score reflecting an individual's genotype status for nine distinct polymorphisms, located within genes such as *PNPLA3*; *TM6SF2*; *HSD17B13*; and *MARC1*.[8] All nine polymorphisms were identified through their association with alcohol-related liver cirrhosis among individuals with high alcohol intake in the UK biobank resource. In the original study, this score showed a reasonable ability to differentiate between individuals in a community setting who go onto develop liver cirrhosis from those who do not (C-index=0.62). In this study, we assess whether the score is useful – either alone or in combination with validated biomarkers - for risk stratification of patients with liver cirrhosis and cured HCV.

The specific polymorphisms and the scoring algorithm for this GRS is indicated in the table below.

rsID	Chr	Gene	Score assigned
rs738409	22	*PNPLA3*	+0.734 for each "G" allele
rs58542926	19	*TM6SF2*	+0.678 for each "T" allele
rs11065484	12	*HNF1A*	+0.275 for each T allele
rs11925835	3	*ARHGEF3*	-0.235 for each T allele
rs28929474	14	*SERPINA*	+0.561 for each "T" allele
rs2954038	8	*TRIB1 region*	+0.160 for each C allele
rs15052	19	*HNRNPUL1*	+0.222 for each C allele
rs2642438	1	*MARC1*	-0.177 for each A allele
rs78542926	4	*HSD17B13*	-0.166 for each TA allele

APPENDIX REFERENCES:

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